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Exceptional Case

Azathioprine as successful maintenance therapy in IgG4-related tubulointerstitial nephritis

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Abstract

A 65-year-old man presented with a progressive increase in plasma creatinine (PCr). Two years before, diffusion-weighted magnetic resonance imaging had revealed a relapse of immunoglobulin G4 (IgG4)-related autoimmune pancreatitis (AIP) associated with sclerosing cholangitis. Bilateral hypointense renal cortical nodules were also described. Kidney biopsy showed patchy disappearance of tubules, sparse interstitial fibrosis and IgG4+ plasma cells (>30 per high power field) leading to the diagnosis of IgG4-related tubulointerstitial nephritis (TIN). Despite methylprednisolone, PCr and serum IgG4 levels remained elevated. Starting azathioprine (AZA) normalized IgG4 levels, which elicited corticosteroid withdrawal after 17 months. One year later, renal function remains stable. Our clinical observation underlines the importance of biological and radiological long-term follow-up of patients with previous AIP in order to early detect IgG4-related renal involvement. Corticosteroids are the first choice, but in the case of adverse effects or partial remission, AZA could be a useful and safe alternative therapy.

Keywords: azathioprine; IgG4-related tubulointerstitial nephritis; plasmocyte

Background

Immunoglobulin G4-related disease (IgG4-RD) is a systemic autoimmune disease first renowned as sclerosing pancreatitis, corresponding to Type 1 autoimmune pancreatitis (AIP). Actually, various organs may be affected. As clinical diagnostic criteria have not been established, an appropriate identification of the disease includes a panel of histological, radiological and biological features currently updated [1, 2]. The pathogenesis of IgG4-RD still remains unclear. An excellent response to corticosteroids is generally observed but there is a high risk of relapse [1, 2].

We report a case of IgG4-related tubulointerstitial nephritis (TIN) occurring 2 years after the relapse of Type 1 AIP. The efficacy of azathioprine (AZA) as corticosteroid-sparing maintenance therapy is underlined.

Case report

A 65-year-old Caucasian man, with a history of Type 1 AIP, was referred to our Nephrology Department because of progressive deterioration of his kidney function (PCr from 79.6 to 124 μmol/L within a time period of 18 months).

He was asymptomatic and his physical examination was unremarkable. Blood tests were as follows: urea: 11.2 mmol/L, haemoglobin: 14.1 g/dL, lipase: 26 IU/L, AST: 15 IU/L, ALT: 11 IU/L, AP: 76 IU/L, γ-glutamyltransferase: 25 IU/L, glucose: 4.88 mmol/L, IgG4: 807 mg/dL, total IgE: 1482 IU/mL, CA 19–9: 37.5 IU/mL, absence of circulating immune complexes and normal complement activity. Estimated glomerular filtration rate was reduced to 36 mL/min/1.73m^2. Urine dipstick analysis showed 1+ of occult blood and 3+ of proteins. Urine sediment only revealed microscopic haematuria (5 red blood cells/high power field) without any significant proteinuria and microalbuminuria (0.26 and 38.0 mg/dL, respectively). The urinary excretion rate of the active form of transforming growth factor-β1 (TGF-β1) was enhanced (996 ng/g Cr) as compared to healthy controls [mean value (minimum–maximum): 31 (19–52) ng/gr Cr]. Reduction in size of both kidneys (8 and 9 cm for right and left sides, respectively) and marked destruction of the renal parenchyma were established by abdominal ultrasonography. Two years before, a diffusion-weighted magnetic resonance imaging (DW-MRI) had demonstrated a relapse of AIP and IgG4-related sclerosing cholangitis. Bilateral hypointense renal cortical nodules had also been described (Figure 1A–C).

Renal biopsy (Figure 1D–F) demonstrated a variable degree of glomerulosclerosis in subcapsular areas. Tubule disappearance was mainly confined to the distal tubules. Intriguingly, interstitial fibrosis was sparse with only few (myo)fibroblasts (Figure 1D). Residues of non-thickened tubular basement membranes neighboured some intact tubules. Plasmocytes and eosinophils infiltrated the medulla, suggesting immunoallergic TIN (Figure 1E). Signs of T cells

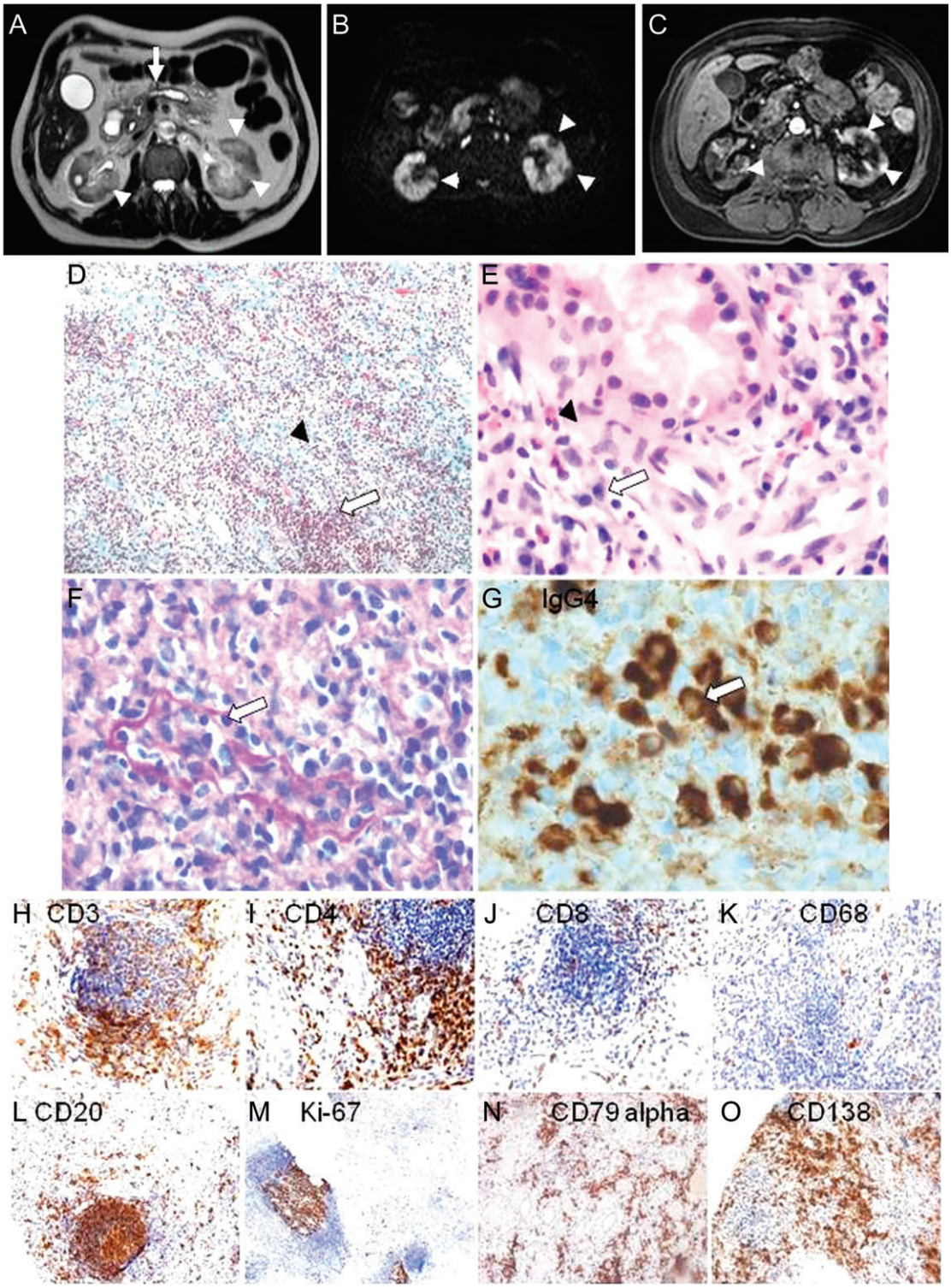

Fig. 1. (**A**) T2-weighted MRI transverse section at the level of the pancreas and kidneys showing main pancreatic duct enlargement (long arrow) and multiple hyperintense nodular areas involving the cortex and medulla of both kidneys (arrowheads). (**B**) DW-MRI ($b = 1000$ mm/s^2) at the same level as (A) showing small nodular hypointense areas of increased water diffusion in both kidneys (arrowheads). (**C**) Arterial phase contrast-enhanced T1-weighted MRI section with fat saturation showing increased uptake (arrowheads) in the nodular areas observed in (A) and (B). (**D**) Renal interstitium massively infiltrated by inflammatory cells (long arrow), with disappearance of tubules and sparse interstitial fibrosis (arrowhead) (Masson's trichrome staining, original magnification ×200). (**E**) Several lymphocytes, plasma cells (long arrow) and numerous eosinophils (arrowhead) infiltrating the renal interstitium (haematoxylin and eosin staining, original magnification ×400). (**F**) Lesions of 'tubulitis' (long arrow) (periodic acid-Schiff staining, original magnification ×400). (**G**) Intracytoplasmic perinuclear IgG4 staining in infiltrating plasma cells IgG4 (long arrow) was found in the subcapsular cortex, in cortical labyrinth and in the medulla (immunoperoxidase staining, original magnification ×1000). (**H**, **I**, **J** and **K**) CD3+, CD4+, CD8+ and CD68+ cells in the periphery of lymphoid nodules, diffusely infiltrating the interstitium. (**L**) Tertiary lymphoid nodules containing CD20+ cells. (**M**) Clusters positive for enhanced nuclear Ki-67 immunostaining forming the germinative centre of tertiary lymphoid organs. (**N** and **O**) CD79 alpha+ and CD138+ cells diffusely infiltrating the cortical interstitium. (H–O) Immunoperoxidase stainings, original magnifications: (H–L) ×200, (M) ×40, (N, O) ×200.

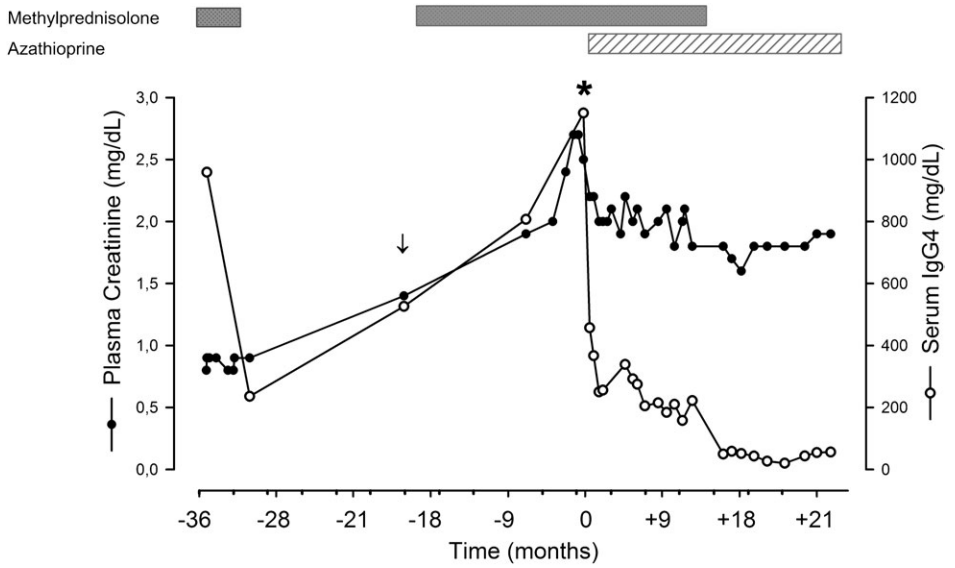

Fig. 2. Time course of plasma creatinine (open circle) and serum IgG4 levels (closed circle). Grey boxes indicate MPS therapy (started at 1 mg/kg/day, followed by progressively tapered doses every 4 weeks) and the hatched box corresponds to AZA administration (2 mg/kg of body weight/day). Arrow indicates the time of DW-MRI and star indicates the time of kidney biopsy (Time 0).

'tubulitis' were noted (Figure 1F). In a 'hotspot' of interstitial inflammation, >30 IgG4+ plasma cells per high power field (×400) were found (Figure 1G). The IgG4 immunostaining was mainly found in interstitial cells corresponding to the intracytoplasmic perinuclear pattern, without any tubular and/or glomerular basement membrane deposits. Some CD4+, CD8+ cells and macrophages (CD68+ cells) diffusely infiltrated the interstitium (Figure 1H–K). Proliferating CD20+ cells formed the germinal centre of so-called 'tertiary lymphoid organs' (TLO) which contained in the marginal zones several CD4+ cells (Figure 1L and M). Several mature plasmocytes (CD79 alpha+ and CD138+ cells) were found in the cortex and medulla (Figure 1N and O). Immunofluorescence of IgG, IgA, IgM, kappa and lambda chains, C1q and C3 was negative (no evidence of glomerular or tubular basement membrane immune complex deposits).

Partial clinical response was obtained with oral methylprednisolone (MPS) therapy (1 mg/kg/day), as PCr and IgG4 levels remained elevated (Figure 2). The introduction of AZA (2 mg/kg/day) normalized IgG4 levels, eliciting the total withdrawal after 17 months. One year later, PCr is stable (1.8–1.9 mg/dL) and IgG4 levels are within the normal range.

Discussion

Our clinical observation underlines the fact that a long-term follow-up of renal function is necessary in patients with AIP in order to early detect IgG4-related TIN especially after disappearance of activity in primarily involved organ(s). Moreover, the present case illustrates that differential diagnostic of plasma cell-rich TIN should integrate IgG4-related TIN.

After princeps cases, series of IgG4-related TIN from Japanese [3] and American [4] populations have been published. Most patients have radiographic abnormalities, described on enhanced computed tomography (CT) as diffuse kidney enlargement, multiple low-density lesions or hypovascular solitary mass [2–4]. Like in our case, Morimoto *et al.* [5] found renal bilateral atrophy on abdominal ultrasonography, but others reported normal-sized unobstructed kidneys with preserved cortical thickness [6] or bilateral swelling [7]. Contrast-enhanced CT scan is probably the most recommended imaging technique for detection of IgG4-TIN lesions [2]. Considering our patient's dysfunction and the risk of iodinated contrast-induced nephropathy, this exam was not performed. However, 4 years before, a CT scan had showed normal kidney structure, except one cyst located on the inferior part of the right kidney. Interestingly, 2 years before the patient's referral for renal evaluation, a DW-MRI demonstrated relapse of AIP associated with sclerosing cholangitis and appearance of bilateral hypointense renal cortical nodules (PCr 1.4 mg/dL).

In Japanese series, concentrations of serum IgG4 correlate with disease activity [3]. A high serum IgG4 level is characteristic of IgG4-TIN but is not sufficient for the diagnosis [8] (elevated serum IgG4 in 92% of patients and 88% of the patients had elevated IgG or IgG4 levels [4]). Nevertheless, the identification of IgG4+ plasma cells in renal biopsy is needed to certify the diagnosis of IgG4-related TIN (100% specificity) [4]. Most cases of IgG4-TIN show interstitial fibrosis, especially with a 'storiform' appearance and thickened tubular basement membranes. These last features were not evident in our case as reported by others [9].

The histological findings of renal TLO formed by infiltrating CD20+ and CD4+ cells support the hypothesis of T helper involvement in physiopathology of IgG4-RD [10]. The high urinary excretion rate of the active form of TGF-β1 measured in our patient is reported to be crucial for maintaining TLO structure and CD4+ cells activation and plays a role in chronic inflammation and renal fibrosis [11].

The optimal immunosuppression regimen (dose and duration) is unknown in IgG4-TIN [1]. Corticosensitivity was reported even 6 years after the first episode of AIP [6]. Recently, Zaidan *et al.* [11] documented a rapid clinical and biological response after rituximab therapy. Mycophenolate mofetil also preserves renal function [4]. To our knowledge, normalization of renal function under AZA was reported only in one case [12]. In our patient, AZA (2 mg/kg/day) and MPS (at decreasing doses) dual therapy maintained PCr value and normalized IgG4 level. During the follow-up period, these positive results persisted 1 year after corticosteroids withdrawal.

In conclusion, in patients presenting with an elevation of PCr and a history of AIP and/or sclerosing cholangitis, IgG4 immunostaining of renal tissue samples is helpful to confirm the diagnosis of IgG4-related TIN. Corticosteroids are the first choice, but in case of adverse effects or partial remission, AZA may be a useful and safe alternative therapy.

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Conflict of interest statement. None declared.

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